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14. ABSTRACT
The goal of this training grant project is to determine whether the prevalence of ATM carriers among prostate cancer patients treated with radiotherapy that develop erectile dysfunction and urinary morbidity is greater than the prevalence of ATM heterozygosity among patients that do not develop this complication. Regardless of the scientific outcome of the proposal the PI will be left with a vast experience in translational research from which to form new hypotheses and research strategies as he begins his career as an independent physician scientist. To assure a well-rounded experience, the school of medicine will insure that the PI will participate for the first two years of the funded period in Mount Sinai's rigorous clinical research training program. The NIH sponsored program will give the PI formal instruction in Clinical Research and Policy Evaluation, Epidemiology and Biostatistics, Basic Science for the Clinical Investigator, Cultural, Illness, and Community Health Outcomes, Behavioral Medicine, and Ethical Issues in Clinical Research. Also the PI, while at Mount Sinai, will make significant progress in establishing collaborative relationships with well-established prostate cancer researchers and will continue this approach in order to expand the scope of the outlined proposal throughout the funding period of this grant.

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Introduction:

A significant proportion of prostate cancer patients treated with radiotherapy develop erectile dysfunction and urinary morbidity induced by exposure to a high dose of radiation. In some cases there are explanations for these reactions, such as doses to large volumes of normal tissue or pre-existing medical conditions such as diabetes or collagen vascular diseases. However, there exists an important subset of patients with no clear explanation for excessive post-treatment morbidity and the potential for a genetic basis must be considered. The purpose of this study is to investigate whether the ATM gene plays a role in this radiation sensitivity. This gene was selected, as the protein it encodes, plays a critical role in the response of cells to irradiation and the repair of radiation-induced damage. Furthermore, cells possessing one mutated copy of this gene are radiosensitive. In addition, the results of a pilot study screening breast cancer patients are supportive of the hypothesis that patients who are carriers of an ATM mutation are more likely to develop radiation-induced complications.

The principal goal of this project is to determine whether men who inherit a mutated copy of the ATM gene are more prone to the development of radiation-induced erectile dysfunction and urinary morbidity. This will be accomplished through comprehensive screening of the ATM gene for germline mutations. If a correlation is found between radiosensitivity and ATM heterozygosity, this would indicate that possession of a mutated copy of the ATM gene results in susceptibility to complications for prostate cancer radiotherapy patients. In addition, a determination will be made as to the pathogenic consequences of each ATM mutation through the use of functional studies that will examine the ability of the ATM protein to act normally in cells from patients who are carriers of a mutation in this gene. This project represents the first study to use the powerful DHPLC mutation screening technique to investigate the association between possession of a mutated ATM gene and both erectile dysfunction and the entire clinical course of a patient's urinary morbidity after treatment with radiation for prostate cancer. It is also the first study to examine whether there is a correlation between the presence of a mutation, development of a radiation-induced complication, and impairment of ATM protein function based upon cellular and molecular analyses.

Body:

My annual report covers the period from 2/1/06 to 1/21/07. I successfully completed the Mount Sinai Clinical Research Training Program, which is sponsored by an NIH K30 Clinical Research Curriculum Award, on 5/30/06. In addition to the training plan, regarding the Clinical Research Training Program, I completed additional coursework offered by Mount Sinai Medical School and was conferred a masters degree in Clinical Research on May 30, 2006. My coursework this year included a thesis, which entailed writing an NIH appropriate grant proposal.

I spent most of the year writing several scientific articles based upon the Mount Sinai experience using low dose rate brachytherapy for the treatment of prostate cancer. The articles fall into several categories. Three articles I worked on with one of my two mentors, Dr. Stock, the chairman of the department, inform our understanding of the natural history of prostate cancer after the treatment by brachytherapy. They are entitled," Changing the patterns of failure for high-risk prostate cancer patients by optimizing local-control", "Disease-specific survival following the brachytherapy management of prostate cancer", and "Biologically effective dose values for prostate brachytherapy: effects on PSA failure and post-treatment biopsy results". All three articles were published this year in our professional journal the International Journal of Radiation Oncology, Biology and Physics. I published two collaborative works with departmental affiliate faculty and a radiation oncology resident entitled, "Low-dose rate prostate brachytherapy is well tolerated in patients with a history of inflammatory bowel disease" and "Urinary symptom flare after brachytherapy for prostate cancer is associated with erectile dysfunction and more urinary symptoms before implantation." (refer to references)

In collaboration with my other mentor, Dr. Barry Rosenstein, I worked on a manuscript writing by another of our residents published this year entitled "Genetic predictors of adverse radiotherapy effects: the Gene-PARE project." This article reviews the relevance of our lab's present work on finding and characterizing genetic predictive markers of radiation sensitivity. (see reference page 12) I have also spent

significant time analyzing and writing about men on whom DHPLC had been performed in the lab of Barry Rosenstein, PhD. At this point approximately 108 of the required 200 patients originally proposed for study accrual have been identified and analyzed within the resources provided in Dr. Rosenstein's lab for this study. I have submitted an article which is presenting in review to the journal of radiation oncology biology and physics entitled, "A GENETICALLY DETERMINED DOSE VOLUME HISTOGRAM PREDICTS FOR RECTAL BLEEDING AMONG PATIENTS TREATED WITH PROSTATE BRACHYTHERAPY." This paper discussed a novel association between rectal bleeding, ATM heterozygosity and radiation dose. (see attached appendix)

Lastly in terms of publications, I have published my first collaborative effort in association with Jan Overgaard's group in Denmark. The publication details an analysis of the ATM gene in patients with severe radiation side effects following radiotherapy for breast cancer. In addition, I have continued to spend 4 hours a week with Simon Hall M.D., the chairman of Urology at Mount Sinai; in the Maury Dean Center for Prostate Health. From these meetings I have continued to solidify my research ties with his faculty. I am working with Natan Bar-Chama MD, an expert in the diagnosis and treatment of erectile function, on a prospective study of the use of sildenafil to prevent brachytherapy induced erectile dysfunction. This trail has become a multi-institutional effort combined with the radiation departments of both Memorial Sloan Kettering and the Beth Israel hospital. In addition, we published an article based upon the preliminary data used for the scientific justification of the study. (refer to references)

I have given two talks at national meetings over the past year regarding my research efforts. At the annual American Society of Therapeutic Radiation Oncology meeting (ASTRO) in November 2006, I gave an oral presentation in the genitourinary toxicity session entitled, "A dose volume histogram for the incidence of rectal bleeding among ATM heterozygotes." In addition to my presentation at ASTRO, I participated to in the formulation and execution of multiple other projected presented by my residents in

training, my research mentors and several junior faculty within the department at the 2006 ASTRO meeting. (see abstracts in attached appendix) At the 11th Annual Scottsdale Prostate Cancer Symposium, March 1-5, 2006, Scottsdale, Arizona I gave a talk entitled, “The Genetics of Radiation Sensitivity.”

In terms of obtaining additional funding opportunities, I am worked with my mentor, Dr. Rosenstein, regarding the submission of an RO-1 grant application in order to be able to continue this work beyond the funded period of the training grant. In the meantime, I continue to benefit from his assistance regarding support in my translational activities.

KEY RESEARCH ACCOMPLISHMENTS:

Completed 24 months of coursework required for Clinicial Research Training Program and received a Masters degree from the Mount Sinai School of Medicine.

I have published this year 3 collaborative works with my clinical mentor Richard Stock, M.D., regarding the natural history of prostate cancer treated with brachytherapy.

I have established a collaborative effort with the Mount Sinai Department of Urology, which has resulted in the publication of a paper. In addition, an ongoing pharmaceutical industry funded effort phase III trial which resulted from this collaborative effort is ongoing.

I have published in collaboration with my other research mentor, Dr. Rosenstein, two articles. One an international collaborative effort with Jan Overgaard's group in Denmark. The other work, in association with a promising resident, details our laboratory's both past and future efforts to identify genetic predictors of radiation sensitivity.

I have published two collaborative works with departmental affiliate faculty and another promising resident works which deepen our understanding of the long-term side effects of radiation therapy in special populations.

I presented my findings regarding my research efforts at an oral presentation at the American Society of Therapeutic Radiation Oncology (ASTRO) annual meeting in Philadelphia, Pennsylvania in November of 2006, and at the 11th Annual International Prostate Cancer Symposium in Scottsdale, Arizona in March of 2006.

REPORTABLE OUTCOMES:

Publications:

Schiff JD, Bar-Chama N, **Cesaretti J**, Stock R. Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function. BJU Int. 2006 Dec;98(6):1255-8.

Lehrer S, **Cesaretti J**, Stone NN, Stock RG. Urinary symptom flare after brachytherapy for prostate cancer is associated with erectile dysfunction and more urinary symptoms before implantation. BJU Int. 2006 Nov;98(5):979-81.

Stock RG, Ho A, **Cesaretti JA,** Stone NN. Changing the patterns of failure for high-risk prostate cancer patients by optimizing local control. Int J Radiat Oncol Biol Phys. 2006 Oct 1;66(2):389-94.

Peters CA, **Cesaretti JA**, Stone NN, Stock RG. Low-dose rate prostate brachytherapy is well tolerated in patients with a history of inflammatory bowel disease. Int J Radiat Oncol Biol Phys. 2006 Oct 1;66(2):424-9.

Ho AY, Atencio DP, Peters S, Stock RG, Formenti SC, Cesaretti JA, Green S, Haffty B, Drumea K, Leitzin L, Kuten A, Azria D, Ozsahin M, Overgaard J, Andreassen CN, Trop CS, Park J, Rosenstein BS. Genetic predictors of adverse radiotherapy effects: the Gene-PARE project. Int J Radiat Oncol Biol Phys. 2006 Jul 1;65(3):646-55.

Andreassen CN, Overgaard J, Alsner J, Overgaard M, Herskind C, **Cesaretti JA**, Atencio DP, Green S, Formenti SC, Stock RG, Rosenstein BS. ATM sequence variants and risk of radiation-induced subcutaneous fibrosis after postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):776-83.

Stock RG, **Cesaretti JA**, Stone NN. Disease-specific survival following the brachytherapy management of prostate cancer. Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):810-6.

Stock RG, Stone NN, **Cesaretti JA**, Rosenstein BS. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and posttreatment biopsy results. Int J Radiat Oncol Biol Phys. 2006 Feb 1;64(2):527-33.

Presentations and Abstracts:

Cesaretti JA. "The Genetics of Radiation Sensitivity." 11th Annual Scottsdale Prostate Cancer Symposium, March 1-5, 2006, Scottsdale, Arizona. (Oral Presentation)

Cesaretti JA. "A dose volume histogram for the incidence of rectal bleeding among ATM heterozygotes." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania. (Oral Presentation)

Stock RG, **Cesaretti JA** and Stone NN. "Patterns of Failure Following the Brachytherapy Management of Prostate Cancer." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania (Oral Presentation)

Peters CA, Stock RG, **Cesaretti JA**, Atencio DP, Peters SR, Burri RJ, Stone NN and Rosenstein BS. "TGFB1 Single Nucleotide Polymorphisms Are Associated With Adverse Quality of Life in Prostate Cancer Patients Treated With Radiotherapy." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania (Resident Oral Presentation)

Burri RJ, Stock RG, Atencio DP, Peters SR, **Cesaretti JA**, Peters CA, Fan G, Stone NN and Rosenstein BS. "Single Nucleotide Polymorphisms in SOD2 and XRCC1 Correlate With the Development of Late Normal Tissue Toxicities in Prostate Cancer Patients Treated With Radiotherapy." ASTRO/Radiation Research Joint Session at the 48th Annual ASTRO meeting, November 2006, Philadelphia, Pennsylvania (Resident Oral Presentation)

Kao J, **Cesaretti JA**, Dumane V, Stone NN and Stock RG. "Improving the Therapeutic Ratio of Prostate Brachytherapy: Dose Escalation in I-125 Prostate Implants." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania (Poster Presentation)

Ho AY, **Cesaretti JA**, Stone NN and Stock RG. "Radiation Dose, Not Treatment Regimen, Is the Most Significant Predictor of Biochemical Control in Patients With Intermediate Risk Prostate Cancer." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania (Resident Poster Presentation)

Terk M, Lo K, **Cesaretti JA**, Stone NN and Stock RG. "Salvage Pd-103 Seed Implantation in the Treatment of Locally Recurrent Prostate Cancer Previously Treated With External Beam Radiation Therapy." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania (Poster Presentation)

Park JL, **Cesaretti JA**, Kao J, Stone NN and Stock RG. "Vardenafil Is More Efficacious Than Tadalafil for Patient's who Requested an Alternative To Sildenafil Following Prostate Brachytherapy." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania (Poster Presentation)

Rosenstein BS, Stock RG, Atencio DP, **Cesaretti JA**, Stone NN and Peters SR. "Use of the Surveyor Nuclease Assay to Identify Genetic Variants Predictive for the Development of Adverse Radiotherapy Effects." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania (Poster Presentation)

CONCLUSIONS:

My professional training as a translational scientist with and emphasis on prostate cancer treatment is progression on several important fronts. I have published several articles in medical research journals this year about prostate cancer treatment outcomes, the side effect profile of prostate cancer treatment and the genetics of radiation sensitivity.

I have continued to expand my collaborative efforts though the prostate health center in the department of urology. A relatively simple clinical outcomes paper published this year has inspired an industry sponsored phase III trial which is ongoing.

I have completed the K30 Physician Research Training Program and have been conferred a Masters degree in May 2006 in Clinical Research from the Mount Sinai School of Medicine.

The results of my research project were presented at the ASTRO annual meeting in addition to the work of my residents, my research mentors and my junior faculty colleagues.

REFERENCES:

Stock RG, Cesaretti JA, Stone NN. “Disease-specific survival following the brachytherapy management of prostate cancer.” Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):810-6.

Andreassen CN, Overgaard J, Alsner J, Overgaard M, Herskind C, Cesaretti JA, Atencio DP, Green S, Formenti SC, Stock RG, Rosenstein BS. “ATM sequence variants and risk of radiation-induced subcutaneous fibrosis after postmastectomy radiotherapy.” Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):776-83.

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Schiff JD, Bar-Chama N, Cesaretti J, Stock R. “Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function.” BJU Int. 2006 Dec;98(6):1255-8.

APPENDICES:

A GENETICALLY DETERMINED DOSE VOLUME HISTOGRAM PREDICTS FOR RECTAL BLEEDING AMONG PATIENTS TREATED WITH PROSTATE BRACHYTHERAPY

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Running title: A genetic DVH for rectal bleeding following prostate brachytherapy.

Supported by Department of the Army grant W81XWH-04-0172 (JAC); American Cancer Society Research Scholar Grant RSGT-05-200-01-CCE (BSR); New York State Empire Clinical Research Investigator Program Grant; New York State Department of Health Contract C017931 (BSR)

Conflict of Interest: Dr. Cesaretti and Dr. Stock serve as consultants for CR BARD. Dr. Stone has a financial interest in Prologics Inc.

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A GENETICALLY DETERMINED DOSE VOLUME HISTOGRAM PREDICTS FOR RECTAL BLEEDING AMONG PATIENTS TREATED WITH PROSTATE BRACHYTHERAPY

JAMIE A. CESARETTI, M.D., M.S.,* RICHARD G. STOCK, M.D.,* DAVID P. ATENCIO, PH.D.,* SHEILA PETERS, B.A.,* CHRISTOPHER A. PETERS, M.D., * RYAN J. BURRI, M.D., *, NELSON N. STONE, M.D., * BARRY S. ROSENSTEIN, PH.D.*†‡§

Departments of *Radiation Oncology, †Community and Preventive Medicine, and ‡Dermatology, Mount Sinai School of Medicine, New York, NY; §Department of Radiation Oncology, New York University School of Medicine, New York, NY.

Purpose: This study examines whether possession of genetic alterations in the ATM (ataxia telangiectasia) gene is associated with rectal bleeding in a dose and volume-dependent manner.

Methods and Materials: 108 prostate cancer patients who underwent brachytherapy using either an ^{125}I implant, a ^{103}Pd implant or the combination of external beam radiotherapy with a ^{103}Pd implant and had a minimum of one year follow-up were screened for DNA sequence variations in the 62 coding exons of the ATM gene using denaturing high performance liquid chromatography. Rectal dose was reported as the volume (cm^3) of rectum receiving the brachytherapy prescription dose. The two-sided Fisher's exact test was used to compare differences in proportions.

Results: A significant correlation between the presence of any ATM sequence alteration and grade 1-2 proctitis was obtained when the radiation dose to rectal tissue was quantified. Rectal bleeding occurred in 4/13 (31%) patients with a variant versus 1/23 (4%) without a genetic alteration for patients who had less than 0.7 cm3 of rectal tissue receiving the implant prescription dose (p=0.05). Of patients in whom 0.7 cm3 - 1.4 cm3 of the rectum received the implant prescription, 4/11 (36%) patients with an ATM alteration exhibited grade 1-2 proctitis, whereas 1/21 (5%) patients without a variant (p=0.04) developed this radiation-induced late effect.

Conclusions: The possession of genetic variants in the ATM gene is associated with the development of radiation-induced proctitis following prostate cancer radiotherapy for patients who receive the full prescription dose to either a low or a moderate volume of rectal tissue.

Key Words:

Genetic predictors, Adverse radiotherapy effects, DVH, Prostate cancer, Brachytherapy.

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Supported by Department of the Army grant W81XWH-04-0172; American Cancer Society Research Scholar Grant RSGT-05-200-01-CCE (BSR); New York State Empire Clinical Research Investigator Program Grant; New York State Department of Health Contract C017931

INTRODUCTION

In the treatment of prostate cancer, the efficacy of the various treatment options is of diminishing importance relative to the side effect profiles, as currently available interventions render similar disease free survival rates (1,2,3). Radiation related side effects are mediated by a number of known patient and treatment related factors. Patient related characteristics include: age, performance status, nutritional state, severity of diabetes, peripheral vascular disease and the functional status of the peri-prostatic organs prior to radiotherapy are known to increase the incidence and severity of radiation related side effects (4,5,6). In regards to treatment related factors, total dose and dose rate of radiation given to the pelvis, rectum, bladder and ejaculatory apparatus are also known to affect the incidence of side effects (7,8,9,10). Recent insight into the etiology of radiation-induced side effects was obtained from RTOG 94-06, which reported a difference in the incidence of late RTOG grade 2 rectal bleeding using 1.8 Gy fractions to 79 Gy and 2.0 Gy fractions to 78 Gy, with the lower dose per fraction affording a 9% incidence compared to a 33% incidence with the higher dose per fraction (11).

With the advent of newer technologies, there is increased interest in decreasing the incidence of side effects. With IMRT and IGRT, dose formalizations used include normal tissue avoidance algorithms, which measurably decrease the incidence of severe normal tissue side effects. Based upon this initial success, there is increased willingness to allow treatment-planning systems to automatically define the dose given to associated structures using conformal avoidance algorithms, rather than simply administering a uniform dose to the prostate gland and adjacent structures (12,13,14,15).

The use of genetic analysis in the formulation of a patient's radiation treatment plan has the potential to further inform the modern practitioner as to the variability and potential severity of side effects observed in prostate cancer. A pilot study of 37 men treated with low-dose-rate brachytherapy revealed statistically significant differences between the incidence of *ATM* alterations and their correlation with rectal bleeding, erectile dysfunction, urinary bother (16). The product encoded by *ATM* plays a central role in mediating the cellular response to radiation-induced DNA damage (20,21). It has long been known that patients with the rare autosomal recessive genetic syndrome ataxia-telangiectasia (A-T) are radiosensitive; in addition, there is expression of other clinically evident sequelae of the syndrome, including cerebellar degeneration, ocular telangiectasias and immunodeficiency (22,23,24). The initial study performed was too small to accurately correlate the incidence of the radiation-related side effects to specific doses given to the peri-prostatic organs. In terms of associating radiation dose-volume

effects to late effects, both the onset of erectile dysfunction and chronic urinary bother have very little precedent for a well-quantified relationship. In contrast, late rectal bleeding does lend itself well to a dose-volume analysis in a relatively small series of patients. Snyder et al. reported that ^{125}I implant patients who received a rectal dose of 160 Gy to more than 1.3 cm^3 of tissue had a higher incidence of rectal bleeding than patients with a small amount of rectal tissue exposed to 160 Gy (17). Refer to figure 1 (reprint with permission). Similar dose response relationships for brachytherapy rectal dose and late rectal bleeding have been defined by other brachytherapists (18,19).

The purpose of this study was to examine the relationship between the genetic status of the ATM gene, rectal dosimetry and rectal bleeding as well as its effect on developing erectile dysfunction.

MATERIAL AND METHODS

Patients

Peripheral blood was obtained from 108 patients seen in routine follow-up following either treatment with a ^{125}I implant, a ^{103}Pd implant or the combination of external beam radiotherapy with a ^{103}Pd implant for treatment of prostate cancer. Patients were staged according to the 1992 American Joint Cancer Commission standard and had biopsy proven prostatic adenocarcinoma (25). Patient and tumor characteristics are outlined in tables 1 and 2. Prostate brachytherapy was performed either directly or under the direct supervision of one radiation oncologist, RGS, using a transrectal ultrasound guided approach to visualize the placement of each radioactive source within the prostate gland through a template guided transperineal needle using the Mick applicator (26). The implant characteristics are outlined on table 3. The prescription doses for ^{125}I, ^{103}Pd, and a combination implant using ^{103}Pd and external beam radiotherapy (45Gy) were 160 Gy, 125 Gy and 100 Gy, respectively (27,28). Patients returned four weeks after the implant for detailed CT-based dosimetric analysis and treatment planning if external beam radiotherapy was given. External beam radiotherapy was given with either 5 field intensity modulated radiation therapy or a 6 field conformal three dimensional plan to a median total dose of 45 Gy. The combination of external beam radiotherapy and brachytherapy has been previously described (29). For this study, a tabular dose volume histogram was available for the rectum of each patient.

Definition of adverse response

The departmental prostate cancer tissue repository database provided all necessary clinical and dosimetric data for this study. The database is an institutional review board (IRB) approved prospective collected resource with data from 2456 patients who have undergone prostate brachytherapy at the Mount Sinai Hospital from June 1990 to March 2006. Every patient had a comprehensive medical history and physical exam prior to the brachytherapy procedure. All patients have been offered continual follow-up evaluations at six-month intervals, which entail a directed history, PSA determination and physical examination. Acute and late rectal toxicity were graded using the Radiation Therapy

Oncology Group (RTOG) morbidity criteria (30). Patients who experienced either RTOG grade level 1 or 2 toxicity were considered to have a radiation related adverse response. Erectile function was physician assessed using the scoring system of 0-complete inability to have erections, 1-able to have erections but insufficient for intercourse, 2-can have erections sufficient for intercourse but considered suboptimal and 3-normal erectile function. The derivation and relevance of this scoring system has been previously described (31, 32). A decrease by two points was defined as a decline in erection function.

For genetic analysis, each patient was approached at the time of follow-up evaluation by a research coordinator who was not involved in the patient's care. An additional IRB approved consent was presented to the patient, beyond the one obtained to collect their clinical data, and consent was obtained for this research study.

ATM exon characterization

DNA isolation from lymphocytes was accomplished using Ficoll separation as described previously (33). PCR was used to amplify each of the 62 exons, and short intronic regions flanking each exon, that comprise the coding region of the *ATM* gene using primers previously described (34). DHPLC analysis was performed on a WAVE Nucleic Acid Fragment Analysis System (Transgenomic, Omaha, NE) using buffer gradient and temperature conditions calculated using WAVEmaker software (version 3.3, Transgenomic) designed for this purpose. Exons with an aberrant DHPLC chromatogram underwent DNA forward and reverse sequencing using an ABI PRISM 377 DNA Sequencer (Foster City, CA).

Statistical analysis

Analyses were performed using the SigmaStat version 3.1 statistical software package. Differences in proportions were derived using the Fisher's exact t test and when appropriate the chi-square statistic. A p value of ≤ 0.05 was considered to indicate statistical significance. In order to compare doses between different isotopes and between the implant alone, and with combined implant and external beam radiotherapy biological equivalent dose calculations were performed as has been previously described (35).

Results

59 *ATM* genetic alterations, representing 25 different variants, were found in the expressed portions of the gene, or within 10 nucleotides of each exon encompassing potential splice sites, in 48 of the 108 patients studied (Table 4). Most of the sequence alterations detected have been previously described (36,37,38) A brachytherapy associated dose response was found for rectal bleeding in this patient population as 10/68 (15%) patients who received the prescription dose to 1.4 cm^3 or less of rectal tissue experienced RTOG grade 1 or 2 late rectal bleeding whereas 14/40 (35%) patients that

received the prescription dose to a larger volume of rectum exhibited rectal bleeding (p=0.03) (figures 2 and 3). However, for patients who received the prescription dose to a similar volume of rectum, an association with the possession of an alteration within *ATM* was observed. For patients whose rectum received less that 0.7 cm^3 of the implant prescription dose, rectal bleeding occurred in 4/13 (31%) patients that had a variant in *ATM*. In contrast, 1/23 (4%) without an alteration in this gene developed rectal bleeding (p=0.05). For patients in whom 0.7 cm^3 - 1.4 cm^3 of the rectum received the implant prescription, 4/11 (36%) patients with an *ATM* alteration exhibited grade 1-2 proctitis, whereas 1/21 (5%) patients without a variant (p=0.04) developed this radiation-induced late effect. There was no statistically significant relationship between possession of *ATM* variants and the development of proctitis for patients in which more than 1.4 cm^3 of the rectum received the prescription dose (figure 4).

24 patients carried missense alterations coding for an amino acid substitution in the ATM protein. No direct association was found on analysis of missense alterations and rectal bleeding. 5/24 (21%) with missense mutations had rectal bleeding versus 20/84 (24%) without an *ATM* alteration (p= 0.97). When only patients with less than 1.5cm^3 exposed to the prescription dose of their radiotherapy, 3/12 (25%) patient's with an *ATM* alteration experiencing rectal bleeding versus 7/56 (13%) (p=0.5). When the silent intronic alteration IVS62+8A→C was added to the group with missense alterations, a significant association was discovered with 9/22 (41%) experiencing late rectal bleeding versus 4/51 (8%) without such mutations in the low rectal dosing range (p=0.002).

A significant decline in erectile function based on missense alteration status was seen among the 68 men who were initially potent prior to radiation therapy. With a median follow-up of 45 months (range: 12-107), 19/68 (28%) experienced a significant decline in erectile function. Among the 14 men with missense alterations, 7/14 (50%) had a significant decline in sexual function, compared to 12/54 (22%) patients without missense alterations (p=0.05). Of interest, 8 patients experienced a biochemical disease relapse, 1/24 (4%) among patients with *ATM* missense alterations and 7/84 (8%) without the alterations (p=0.8). The variables known to affect either prostate cancer treatment outcome or late toxicity were evenly distributed among patients with and without an *ATM* sequence alteration (table 5).

Discussion

A significant dose volume effect was found for the incidence of rectal bleeding within this group of 108 patients treated with brachytherapy for prostate cancer. At the low end of rectal radiation dose exposure, a significant difference was identified for patients who received the radiation prescription dose to between 0.1 cm^3 and 0.7 cm^3 of rectal tissue.

This relationship was again seen in the next dose level of 0.7 cm^3 to 1.4cm^3. For patients who received the prescription dose to greater than 1.4 cm^3, there was no longer a difference between the incidence of rectal bleeding among patients with and without an *ATM* variant. Based upon these results, it is possible to conclude that the slight difference in radiosensitivity conferred by the presence of a variant in *ATM* was of consequence only when a limited volume of rectal tissue was irradiated. Once a threshold in volume receiving the prescription dose had been reached, the genetic status of an individual patient had little effect on the likelihood of developing rectal bleeding.

The mechanism of injury responsible for late radiation induced rectal injury occurs mainly in the submucosal region while acute injury is a transient mucosal phenomenon. Late radiation injury is caused by progressive fibrosis with both the deposition of collagen and fibroblast proliferation noted in the rectal wall. Microvascular injury also occurs and manifests clinically as the appearance of telangectasias upon the rectal surface. If the submucosal region becomes very ischemic, ulceration develops and a fistula can form, although rarely (39,40,41). In the vast majority of patients, bleeding resolves in a few months without further intervention. In addition, radiation oncologists have lowered the incidence of fistulas by cautioning the care team to avoid biopsy of such regions and to adhere to a conservative observation management policy (42).

In terms of ED, a relationship was found between its development and the presence of *ATM* missense variants. There is some controversy regarding the precise etiology of radiation induced ED in that it can either be attributed to the well known surgical cause, damage to the bilateral neurovascular bundles, or to large vessel fibrosis and damage (43,44). It is tempting to hypothesize that the etiology is microvascular in the sense that it is mimicking the apparent mechanism of injury seen in the progression to rectal bleeding. One could hypothesize that a dose response might become apparent between its onset and the dose to the posterolateral neurovascular bundles if one were able to censure from a studied population those who are genetically predisposed to ED. Because our treatment policy regarding brachytherapy seed insertion does not allow for placement of a radiation source below the urogenital diaphragm, measurable dose to these structures does not occur. This finding will provide for a future investigation informed by the genetic data to identify possible periprostatic radiotherapy targets which may be causally attributed to erectile dysfunction incidence.

When exposed to ionizing radiation, cells arrest their progression through the cell cycle allowing for repair of DNA damage. Much is known about the molecular events that orchestrate the response of the cell to radiotherapy-induced damage. An early event is the formation of the MRE11-RAD50-NBS1 (MRN) complex, which causes the recruitment of the ATM protein. The ATM protein then acts by interacting with various substrates to halt the cell cycle progression in the G1, S and G2 phases of mitosis. The molecules responsible for these regulatory steps include p53, CHK1, CHK2, MDM2, BRCA1, MDC1, and 53BP1 (45,46). It is reasonable to hypothesize that if exacerbated normal tissue effects are observed within the radiation dose range which is well tolerated by the majority of patients, a similar magnification of the radiation effect is likely to occur within the sensitive individual's cancer cell. The hypothesis of improved cancer

prognosis as a consequence of extreme late radiation normal tissue side effects has been tested in terms of breast cancer without success (47). Prostate cancer is a slow growing local phenomenon in the majority of patients with local cure conferring long-term systemic cure (48). This is not the case regarding breast cancer, which has since the mid-1970's been thought to be a systemic disease from onset (49). Though radiotherapy does confer a dramatic local control benefit in the setting of breast conservation, only recently has a survival advantage been apparent based upon the analysis of 42,000 patients with the use of radiotherapy (50). In our series, only 8 patients have experienced biochemical relapse, 1/24 (4%) among patients with ATM missense alterations and 7/84 (8%) without alterations. As our patient series continues to mature and increase in size the initial numerical, difference seen in our series holds the possibility of a statistical difference in the future.

Conclusion

The possession of genetic variants in the *ATM* gene is associated with the development of radiation-induced proctitis following prostate cancer radiotherapy for patients who receive the full prescription dose to either a low or a moderate volume of rectal tissue. This finding supports the hypothesis that a genetically determined dose-response relationship is possible and could be used to predict the probability of side effects associated with radiotherapy, and serve as a rational basis for individualized radiation dose prescriptions.

REFERENCES

1. Stock RG, Cesaretti JA, Stone NN. Disease-specific survival following the brachytherapy management of prostate cancer. Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):810-6.

2. Zelefsky MJ, Chan H, Hunt M, et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol. 2006 Oct;176(4 Pt 1):1415-9.

3. Zhou P, Chen MH, McLeod D, et al. Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Clin Oncol. 2005 Oct 1;23(28):6992-8.

4. Stone HB, Coleman CN, Anscher MS, et al. Effects of radiation on normal tissue: Consequences and mechanisms. Lancet Oncol 2003;4:529 –536.

5. Bentzen SM, Overgaard J. Patient-to-patient variability in the expression of radiation-induced normal tissue injury. Semin Radiat Oncol 1994;4:68–80.

6. Jackson A, Kutcher GJ, Yorke ED. Probability of radiation induced complications for normal tissues with parallel architecturesubject to non-uniform irradiation. Med Phys 1993; 20:613– 625.

7. Diaz A, Roach M, Marquez C et al., Indications for and the significance of seminal vesicle irradiation during 3D conformal radiotherapy for localized prostate cancer, Int J Radiat Oncol Biol Phys 30 (1994), pp. 323–329.

8. Zelefsky MJ, Cowen D, Fuks Z et al., Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma, Cancer 85 (1999), pp. 2460–2468.

9. Pilepich MV, Asbell SO, Krall JM et al., Correlation of radiotherapeutic parameters and treatment-related morbidity Analysis of RTOG study 7706, Int J Radiat Oncol Biol Phys 13 (1987), pp. 1007–1012.

10. Lee WR, Hanks GE, Hanlon AL et al., Lateral rectal shielding reduces late rectal morbidity following high-dose three-dimensional conformal radiation therapy for clinically localized prostate cancer further evidence for a significant dose effect, Int J Radiat Oncol Biol Phys 35 (1996), pp. 251–257.

11. Michalski JM, Winter K, Purdy JA et al. Toxicity after three-dimensional radiotherapy for prostate cancer on RTOG 9406 dose Level V. Int J Radiat Oncol Biol Phys. 2005 Jul 1;62(3):706-13.

12. Jani AB, Su A, Correa D et al. Comparison of late gastrointestinal and genitourinary toxicity of prostate cancer patients undergoing intensity-modulated versus conventional radiotherapy using localized fields. Prostate Cancer Prostatic Dis. 2006 Sep 19;

13. Sanguineti G, Cavey ML, Endres EJ et al. Does Treatment of the Pelvic Nodes with IMRT Increase Late Rectal Toxicity over Conformal Prostate-Only Radiotherapy to 76 Gy? Strahlenther Onkol. 2006 Sep;182(9):543-549.

14. Kupelian PA, Thakkar VV, Khuntia D et al. Hypofractionated intensity-modulated radiotherapy (70 gy at 2.5 Gy per fraction) for localized prostate cancer: long-term outcomes. Int J Radiat Oncol Biol Phys. 2005 Dec 1;63(5):1463-8.

15. Xia P, Pickett B, Vigneault E et al. Forward or inversely planned segmental multileaf collimator IMRT and sequential tomotherapy to treat multiple dominant intraprostatic lesions of prostate cancer to 90 Gy. Int J Radiat Oncol Biol Phys. 2001 Sep 1;51(1):244-54.

16. Cesaretti JA, Stock RG, Lehrer S et al. ATM sequence variants are predictive of adverse radiotherapy response among patients treated for prostate cancer. Int J Radiat Oncol Biol Phys. 2005 Jan 1;61(1):196-202.

17. Snyder KM, Stock RG, Hong SM et al. Defining the risk of developing grade 2 proctitis following 125I prostate brachytherapy using a rectal dose-volume histogram analysis. Int J Radiat Oncol Biol Phys. 2001 Jun 1;50(2):335-41.

18. Waterman FM, Dicker AP. Probability of late rectal morbidity in 125I prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2003 Feb 1;55(2):342-53.

19. Tran A, Wallner K, Merrick G et al. Rectal fistulas after prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2005 Sep 1;63(1):150-4.

20. Savitsky K, Bar-Shira A, Gilad S, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science 1995;268:1749-1753.

21. Shiloh Y. ATM and related protein kinases: safeguarding genome integrity. Nat Rev Cancer 2003;3:155-168.

22. Telatar M, Wang Z, Udar N, et al. Ataxia-telangiectasia: mutations in ATM cDNA detected by protein-truncation screening. Am J Hum Genet 1996;59:40-44.

23. Morgan JL, Holcomb TM, Morrissey RW. Radiation reaction in ataxia-telangiectasia. Am J Dis Child 1968;116:557–558.

24. Gatti RA, Tward A, Concannon P. Cancer risk in ATM heterozygotes: a model of phenotypic and mechanistic differences between missense and truncating mutations. Mol Genet Metab 1999;68:419-423.

25. American Joint Committee on Cancer. Cancer staging manual, Lippincott, Philadelphia (1992).

26. Stock RG, Stone NN, Wesson MF, et al. A modified technique allowing interactive ultrasound guided three dimensional transperineal prostate implantation. Int J Radiat Oncol Bio Phys 1995;32:219–225.

27. Nath R, Anderson LL, Luxton G, et al. Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43. Med Phys 1995;22:209–234.

28. Williamson JF, Coursey BM, DeWerd LA, et al. Recommendations of the American Association of Physicists in Medicine on 103Pd interstitial source calibration and dosimetry: implications for dose specification and prescription. Med Phys. 2000 Apr;27(4):634-42.

29. Stock RG, Stone NN, Cesaretti JA et al. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and post-treatment biopsy results. Int J Radiat Oncol Biol Phys. 2006 Feb 1;64(2):527-33.

30. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–1346.

31. Stock RG, Stone NN, Iannuzzi CM. Sexual potency following interactive ultrasound-guided brachytherapy for prostate cancer. Int J Radiat Oncol Biol Phys 1996;35:267-273.

32. Stock RG, Kao J, Stone NN. Penile erectile function after permanent radioactive seed implantation for treatment of prostate cancer. J Urol. 2001;165:436-439.

33. Atencio DP, Iannuzzi CM, Green S, et al. Screening breast cancer patients for ATM mutations and polymorphisms by using denaturing high-performance liquid chromatography. Environ Mol Mutagen 2001;38:200-208.

34. Bernstein JL, Teraoka S, Haile RW, et al. WECARE Study Collaborative Group. Designing and implementing quality control for multi-center screening of mutations in the ATM gene among women with breast cancer. Hum Mutat 2003;21:542-550.

Stock RG, Stone NN, Cesaretti JA, et al. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and post-treatment biopsy results. Int J Radiat Oncol Biol Phys. 2006 Feb 1;64(2):527-33.

36. Sommer SS, Buzin CH, Jung M, et al. Elevated frequency of ATM gene missense mutations in breast cancer relative to ethnically matched controls. Cancer Genet Cytogenet 2002; 134:25–34.

37. Sommer SS, Jiang Z, Feng J, et al. ATM missense mutations are frequent in patients with breast cancer. Cancer Genet Cytogenet 2003;145:115–120.

38. Thornstenson YR, Shen P, Tusher VG, et al. Global analysis of ATM polymorphism reveals significant functional constraint. Am J Hum Genet 2001;69:396–412.

39. O'Brien PC. Radiation injury of the rectum. Radiother Oncol 2001;60:1–14.

40. Hopewell JW, Calvo W, Jaenke R, et al. Microvasculature and radiation damage. Recent Results Cancer Res 1993; 130:1–16.

41. Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: A predictor for late radiation morbidity. Int J Radiat Oncol Biol Phys 1999;43:475– 479.

42. Stone NN, Stock RG. Complications following permanent prostate brachytherapy. Eur Urol 2002;41:427– 433.

43. Walsh PC, Mostwin JL. Radical prostatectomy and cystoprostatectomy with preservation of potency. Results using a new nerve-sparing technique. Br J Urol. 1984 Dec;56(6):694-7.

44. Zelefsky, M. J. and Eid, J. F. Elucidating the etiology of erectile dysfunction after definitive therapy for prostatic cancer. Int J Radiat Oncol Biol Phys, 40: 129-133, 1998.

45. Pawlik TM, Keyomarsi K. Role of cell cycle in mediating sensitivity to radiotherapy. Int J Radiat Oncol Biol Phys. 2004 Jul 15;59(4):928-42. Review.

46. Khanna KK, Lavin MF, Jackson SP, Mulhern TD. ATM, a central controller of cellular responses to DNA damage. Cell Death Differ. 2001 Nov;8(11):1052-65. Review.

47. Meyer A, John E, Dork T, et al. Breast cancer in female carriers of ATM gene alterations: outcome of adjuvant radiotherapy. Radiother Oncol. 2004 Sep;72(3):319-23.

48. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am. 2001 Aug;28(3):555-65. Review.

49. Fisher B. From Halsted to prevention and beyond: advances in the management of breast cancer during the twentieth century. Eur J Cancer. 1999 Dec;35(14):1963-73. Review.

50. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005 Dec 17;366(9503):2087-106. Review.

63 A Genetically Determined Dose Volume Histogram Predicts for Rectal Bleeding Among Patients Treated With Prostate Brachytherapy

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Purpose/Objective(s): The purpose of this study was to examine whether possession of genetic alterations in the *ATM* (mutated in ataxia telangiectasia) gene is associated with rectal bleeding in a dose and volume-dependent manner.

Materials/Methods: 114 patients with a minimum of 1 year follow-up who underwent low dose rate brachytherapy using either an ^{125}I implant, a ^{103}Pd implant or the combination of external beam radiotherapy with a ^{103}Pd implant for treatment of prostate cancer were screened for DNA sequence variations in all 62 coding exons of the *ATM* gene using denaturing high performance liquid chromatography. The RTOG scaled rectal toxicity and post-implant rectal dose volume histogram for each genetically characterized patient was obtained from a prospective database. Rectal dose was reported as the volume of the rectum receiving the brachytherapy prescription dose. The prescription doses for ^{125}I, ^{103}Pd, and a combination implant using ^{103}Pd and external beam radiotherapy were 160 Gy, 125 Gy and 100 Gy. Erectile function was assessed using a physician assigned score (0 - no erections, 1 - erections insufficient for intercourse, 2 - erections suitable for intercourse, 3 - normal function). The two-sided Fisher's exact test was used to compare differences in proportions.

Results: 62 *ATM* DNA alterations were identified in 52 patients. 30 of the alterations encoded for non-conservative amino acid changes in the ATM protein in 28 patients. The median follow-up time was 36 months (range: 12-71). A significant correlation between the presence of any *ATM* sequence alteration and grade 1-2 proctitis was obtained when controlling for rectal volume. Rectal bleeding occurred in 4/14 (29%) patients with a variant versus 1/25 (4%) without a genetic alteration for patients who had less that 0.7 cm^3 of rectal tissue receiving the implant prescription dose (p_0.05). For patients in which 0.7 cm^3 - 1.4 cm^3 of the rectum received the implant prescription, 8/15 (53%) patients with an *ATM* alteration exhibited grade 1-2 proctitis, whereas 3/20 (15%) patients without a variant (p_0.03) developed this radiation-induced late effect. There was no statistically significant relationship between possession of *ATM* variants and the development of proctitis for patients in which more than 1.4 cm^3 of the rectum received the prescription dose. Of patients who were at risk for developing erectile dysfunction (ED), 12/22 (54%) with missense alterations displayed prospectively evaluated ED as opposed to 8/57 (14%) without a sequence alteration (p_0.01).

Conclusions: The possession of genetic variants in the *ATM* gene is associated with the development of radiation-induced proctitis following prostate cancer radiotherapy for patients who received the full prescription dose to either a low or moderate volume of rectal tissue. This finding supports the contention that a genetically determined dose-response relationship is possible and could be used to better predict the probability of side effects associated with radiotherapy. Hence, use of this type of predictive assay may serve as a rational basis for individualized radiation dose prescriptions.

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103 **Patterns of Failure Following the Brachytherapy Management of Prostate Cancer**

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Purpose/Objective(s): Although long term biochemical control rates are emerging following the brachytherapy management of prostate cancer, little information is available on the patterns of failure for those with PSA failure. This report examines local and distant recurrence patterns in these patients and the factors that affect them.

Materials/Methods: From 1990 to 2006, 2,456 patients underwent low dose rate brachytherapy as part of their management for T1-T3 prostate cancer from a single institution. Of these patients, 54%, 22% and 33% were low, intermediate and high risk at presentation. Patients were treated with a real time ultrasound guided technique with intraoperative planning. There were three main treatment groups (based on risk): implant alone (PD-103 or I-125), implant and hormonal therapy or trimodality (hormonal, brachy and external beam therapy). During this time period, 184 patients (7%) experienced a biochemical failure (ASTRO definition). These patients were followed from 26 to 184 months (mos)(median - 82). 106/184 patients underwent post-treatment prostate biopsy 2 or more years post implant. Local failure was defined as a positive biopsy post-treatment. Distant metastases were defined as bone, visceral organ or nodal disease outside the pelvis.

Results: PSA failure patients were low risk in 22%, intermediate in 14% and high risk in 64%. The PSA doubling time (DT) for these patients were _ 3 mos in 21%, _3 - 6 mos in 17%, _ 6-10 mos in 16% and _ 10 mos in 84%. No patient developed a clinical local recurrence based on an abnormal digital rectal examination. 34% (36/106) had positive post - treatment biopsies. The following factors predicted for a positive biopsy: PSA DT - _ 3 mos (0%), _3-6 mos (0%), _6-10 mos (30%) and _10 mos (49%) (p_0.001); BED - _ 150 (44%), _150 (24%) (p_0.03), treatment - implant alone (45%), implant _ hormones (37%), trimodality (0%) (p_0.0001). The actuarial freedom from developing distant metastases rate (FFDM) at 10 years was 76%. Of the 37 patients with clinical metastases, 14 underwent post-treatment biopsy and all were negative. The following factors predicted for FFDM at 10 years: PSA DT - _ 3mos (22%), _ 3-6 mos (66%), _ 6-10 mos (84%), _10 mos (92%) (p_0.0001); time to PSA failure -_ 1 year (58%), _1 - 2 years (65%), _2-3years (78%) and _ 3 years (96%) (p_0.0001); Gleason score - _ 6 (89%), 7 (75%), 8-10 (50%)(p_.0001); risk group - low (85%), intermediate (96%), high (69%) (p_0.01); treatment - implant alone (93.5%), implant _hormones (88.5%); trimodality (35%) (p_0.0001).

Conclusion: High risk patients make up the majority of biochemical failures. Local failure based on biopsy was identified in about one third of patients and was most common in those with long DT and low BED implants. One quarter of PSA failure patients developed distant metastases within 10 years post- treatment and this was most commonly seen in those with short DT, early PSA recurrence and high grade tumors. The remaining patients remain in determinant as to the source of their rising PSA.

Author Disclosure: R.G. Stock, BARD, F. Consultant/Advisory Board; J.A. Cesaretti, BARD, F. Consultant/Advisory Board; N.N. Stone, Prologics, E. Ownership Interest.

121 ***TGFB1* Single Nucleotide Polymorphisms Are Associated With Adverse Quality of Life in Prostate Cancer Patients Treated With Radiotherapy**

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Purpose/Objective(s): TGF_1, the protein encoded by *TGFB1*, is a key cytokine that is associated with proliferation, differentiation and deposition of extracellular matrix proteins in irradiated cells. The purpose of this study was to investigate whether the presence of single nucleotide polymorphisms (SNPs) located within *TGFB1* might be predictive for the development of adverse quality of life outcomes in prostate cancer patients treated with radiotherapy.

Materials/Methods: 133 patients diagnosed with clinically localized prostate cancer and a minimum of 1-year follow-up who underwent definitive low-dose-rate brachytherapy alone or in combination with external beam radiotherapy were screened for SNPs in *TGFB1* using DNA sequencing. Three quality of life outcomes were investigated: (1) prospective decline in erectile function (patients using hormone therapy were censored from this analysis) using both the previously described Mount Sinai Erectile Function Scale (MSEFS) and the IIEF-5; (2) urinary irritation using the quality of life measure on the International Prostate Symptom Score (IPSS); and (3) rectal bleeding using the RTOG/EORTC late morbidity scoring scale. Statistical analysis was performed using the chi-square test to compare the groups with respect to developing adverse quality of life measures. Median follow-up was 39.5 months (range 12-108 mo, SD_21.6).

Results: Those patients who were either homozygous for the -509 C_T, homozygous for the 869 T_C (leu_pro), or heterozygous for the 915 G_C (arg_pro) SNPs, were significantly associated with developing a prospective decline in erectile function compared to those that did not harbor any of these SNPs; 50% (8/16) versus 20% (8/40, p_0.02). In addition, patients homozygous for the -509 C_T SNP had a significantly increased risk of developing late RTOG grade 1 or 2 rectal bleeding compared with those not homozygous for this SNP; 44% (4/9) versus 18% (22/124, p_0.05). There were no statistically significant correlations with *TGFB1* SNPs and the development poor urinary quality of life. There were no significant correlations with prostate D90 or rectal v100 with the development of ED or rectal bleeding.

Conclusions: Possession of certain *TGFB1* SNPs is associated with the development of both erectile dysfunction and late rectal bleeding in patients treated with radiotherapy for prostate cancer. Therefore, identification of patients harboring these genetic alterations may represent a means to predict which men are most likely to suffer from poor quality of life outcomes following radiotherapy for prostate cancer.

178 **Single Nucleotide Polymorphisms in *SOD2* and *XRCC1* Correlate With the Development of Late Normal Tissue Toxicities in Prostate Cancer Patients Treated With Radiotherapy**

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Full abstract will be published in the Radiation Research Society's Final Program.

2203 Improving the Therapeutic Ratio of Prostate Brachytherapy: Dose Escalation in I-125 Prostate Implants

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Background: There has been significant interest in dose escalation using external beam radiation for prostate cancer. In contrast, the safety and efficacy of doses above the ABS recommended D90 of 145 Gy using brachytherapy has not been established.

Purpose/Objective(s): The purpose of this study is to characterize the oncologic results and toxicity profile of patients treated with a D90 of _180 Gy.

Materials/Methods: At Mount Sinai, the prescription D90 for I-125 monotherapy has been 160 Gy (TG-43), using real-time intraoperative planning since 1997. Consequently, some patients have a D90 of _180 Gy at the time of post-implant dosimetry. From 6/1995 to 2/2004, 598 patients were treated with I-125 alone for T1–2 prostate cancer with a D90 of _180 Gy (median 197, range 180 - 267). The implants were performed using a real-time ultrasound guided seed placement method, intraoperative dosimetry and modified peripheral loading to optimize target coverage and homogeneity. A median of 92 seeds (range 31 to 220) were implanted into a prostate with a median US volume of 44.0 cc (range 14.3–125.0cc). The median activity implanted was 44.6 mCi (range 7.6 –96.9 mCi) and the median V150 was 70.7% (range 21.0 –94.1%). The median urethral D30 was 240.0 Gy (range 2.4 –515.5 Gy) and the median rectal V100 was 1.00 cc (range 0.00–6.19 cc). The biochemical control of 435 patients that had a minimum 2 year PSA follow-up (median f/u 6.7 years; range 2.0 –11.1 years) was analyzed. 9.2% of the patients were intermediate or high risk based on one or more of the following factors: PSA_10, Gleason 7–10 or T2c disease. 31% received neoadjuvant hormonal therapy. Of the 509 patients with available potency data, 375 (73.7%) were potent prior to implant. Longitudinal urinary function was assessed in 249 patients with pretreatment IPSS and a follow-up IPSS at least 3 years after implant (median 4.5 years, range 3–10 years). Post-brachytherapy prostate biopsy results were available for 120 (20.1%) patients.

Results: The 5 year bDFS (ASTRO definition) for the entire cohort was 96.6%. The positive biopsy rate was 4.1%. For low risk patients, the 5 year bDFS was 97.1% while for intermediate/high risk patients, the 5 year bDFS was 92.6%. There were no PSA failures beyond 6 years. Freedom from _ grade 2 rectal bleeding at 5 years was 88.5%. Acute urinary retention occurred in 10.7%, more commonly in patients with high pretreatment IPSS scores (p_0.01). The median IPSS scores increased significantly during the first six months after implant. The median IPSS was 6 (range 0–28; 25 to 75th percentile: 3–10) pre-implant compared to 6 (range 0–31; 25 to 75th percentile: 3–11) post-implant with 3-year minimum follow-up. Using a 2-tailed t-test with unequal variance, there were no significant differences between pre and post-implant IPSS scores (p_0.14). Among patients who were potent prior to treatment, 73.4% remained potent at 5 years after implant.

Conclusions: Patients with a minimum D90 of 180 Gy had outstanding local control based on PSA control and biopsy data. The absence of late failures with extended follow-up suggests durable tumor control. The toxicity profile, particularly long-term urinary and sexual function, was excellent and demonstrates that D90 doses _180 Gy are well tolerated.

2247 **Radiation Dose, Not Treatment Regimen, Is the Most Significant Predictor of Biochemical Control in Patients With Intermediate Risk Prostate Cancer**

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Purpose/Objective(s): To evaluate the influence of treatment-related factors on the biochemical freedom from failure rate in patients with intermediate-risk prostate cancer.

Materials/Methods: From a prospectively collected database of men treated with low dose rate brachytherapy for prostate cancer between 1990 to 2003, 494 patients with either one or two intermediate-risk features (PSA 10–20 ng/ml, Gleason 7 or Stage T2b) were identified who had a minimum of 24 months follow-up. For every patient, the dose delivered to the prostate was calculated using a 1-month post-implant CT-based dosimetric analysis. In addition, biologically equivalent dose (BED) values were calculated in order to compare doses from different isotopes and treatment regimens. Patients were treated with either brachytherapy alone (Pd-103 or I-125) or in combination with 3 to 9 months of hormone therapy and/or external beam radiotherapy. Patient-related and treatment-related factors were analyzed with respect to their effect on freedom from biochemical failure (FFbF). The median follow-up for the 494 eligible patients was 55 months (range 48–153). Biochemical failure was defined by the ASTRO consensus definition. Univariate and multivariate Cox regression analysis was used to determine if any variables were predictive of FFbF. A two-sided p value _ 0.05 was considered significant.

Results: The FFbF at 10 years was 90%. On univariate analysis, stage, the use of hormonal therapy, number of intermediate-risk factors, treatment type (implant alone, implant with hormones, implant and EBRT, trimodality therapy) and BED (_120, _120–140, _140–160, _160–180, _180–200, _200), were significant (p_0.05). Multivariate analysis identified BED as the only significant factor predictive for FFbF (p_.015). The FFbF rates at 10 years for BED _120, _120–140, _140–160, _160–180, _180–200, _200 were 65%, 79%, 89%, 90%, 94% and 93%, respectively (p_0.00). Cox regression analysis of patients with a minimum BED_140 (n_444) revealed that other treatment, patient and disease-related variables did not impact FFbF. In this high dose subset of patients, treatment type did not affect biochemical control, with 10-year FFbF rates of 85.1%, 94.5%, 94.6% and 93.8% in patients who received implant alone (n_56), implant and hormones (n_165), combined implant and EBRT (n_47) and trimodality therapy (n_176), respectively (p_0.78).

Conclusions: Radiation dose (BED) is the most important predictor of FFbF following prostate brachytherapy in the management of patients with one or two intermediate-risk factors. In patients who received BED_140, the addition of external beam to brachytherapy did not improve outcome. High dose implant _/- hormonal therapy, combined implant and EBRT and trimodality therapy are all viable treatment options for intermediate-risk prostate cancer patients. Treatment regimens should continue to be individualized based on presenting disease characteristics, until results from the RTOG 0232 prospective trial become available.

2271 **Salvage Pd-103 Seed Implantation in the Treatment of Locally Recurrent Prostate Cancer Previously Treated With External Beam Radiation Therapy**

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Purpose/Objective(s): Studies have shown that local failure rates following external radiation therapy range between 25–32%. In past years, treatment options for these patients were somewhat limited and included long-term hormone therapy as well as potentially morbid salvage prostatectomy.

Materials/Methods: This is a retrospective review of 65 consecutive men treated at 2 institutions with salvage Pd-103 prostate seed implants between May 1992 and June 2004. All men had previously been treated with external radiation with doses ranging from 6300cGy - 7380 cGy. All had biopsy proven disease in the prostate with negative CT scan and Bone scan staging studies. All men were treated with a Real-Time Intra-Operative Dosimetry Technique. 95% of men received short term neoadjuvant hormonal therapy with an LHRH agonist. Serial PSA levels were obtained at follow-up and treatment related toxicities were recorded according to the RTOG late toxicity grading scale. Biochemical failure was defined according to the ASTRO Consensus definition of 3 consecutive rises in PSA.

Results: The median follow-up from time from the implant was 38 months (range 11 - 125 months). 65% of men are free from biochemical relapse. Five patients required a TURP for persistent urinary obstruction. One patient developed hemorrhagic cystitis and one patient developed a recto-urethral fistula requiring a colostomy.

Conclusions: This large series demonstrates that brachytherapy is a potentially good salvage option for patients with locally recurrent prostate cancer following external beam radiation therapy. Using a Real-Time Intra-Operative Dosimetry Technique, Grade 3 and 4 late toxicity rates were low, documenting the safety of this procedure. Care must be made to limit the dose to the rectum.

2593 **Vardenafil Is More Efficacious Than Tadalafil for Patient's who Requested an Alternative To Sildenafil Following Prostate Brachytherapy**

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Purpose/Objective(s): To evaluate the relative impact of either tadalafil or vardenafil as second-line treatment following sildenafil for the treatment of prostate brachytherapy associated erectile dysfunction.

Materials/Methods: 54 patients with localized prostate cancer and median age of 63 years (range: 42–74) were treated with brachytherapy from 10/1995 to 6/2004. All patients were initially treated for erectile dysfunction (ED) with sildenafil followed by either vardenafil or tadalafil. Median follow-up after brachytherapy with prospective quality of life measures was 4.1 years (range 0.6 to 9.3 years). Erectile function (EF) was assessed using a physician assigned score (0 - no erections, 1 - erections insufficient for intercourse, 2 - erections suitable for intercourse, 3 - normal function) and beginning in June of 2000, the validated five question International Index of Erectile Function (IIEF-5) was used as a complimentary method to quantify late EF. Detailed notes were made regarding pharmacological intervention for EF on a standardized data collection form. The Pearsons chi-square test and Student t-test were used to compare groups.

Results: The median time to the first use of sildenafil from radiotherapy was 1.6 years (range 0.4 to 8.1). 35% (19/54) used sildenafil consistently for _12 months during their course of follow-up. 24% (13/54) were given a prescription for vardenafil and 76% (41/54) were given a prescription for tadalafil. 31% (4/13) of patients treated with vardenafil and 32% (13/41) of patients treated with tadalafil reported a physician assigned EF rise of 1 or more in the next follow-up period (p_0.95). 9% (1/11) of men taking vardenafil experienced a decline in IIEF-5 versus 42% (14/33) of men taking tadalafil (p_0.04). In contrast 33% (3/9) patients taking vardenafil and 0% (0/23) using tadalafil experienced a rise in IIEF-5 above 20 (p_0.001). The mean rise in the IIEF-5 of the vardenafil group was 3.7 (95%CI:2.3–9.7) versus 0.4 (95%CI:3.6–4.4) for the tadalafil group (p_0.04).

Conclusions: Approximately 1/3 of patients have a clinically significant response to tadalafil or vardenafil as second line ED treatment following brachytherapy. Based on a hypothesis generating analysis of patient reported questionnaires, vardenafil has a more significant positive impact on sexual health than tadalafil following patient disaffection with sildenafil for brachytherapy induced ED. Further investigation of these agents in radiation-induced ED is warranted.

2673 Use of the Surveyor Nuclease Assay to Identify Genetic Variants Predictive for the Development of Adverse Radiotherapy Effects

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Purpose/Objective(s): The goal of our research program is to identify genetic variants (single nucleotide polymorphisms and rare variants) that are predictive for the development of adverse effects associated with radiotherapy. In order to achieve this goal, an assay with a high level of sensitivity and specificity for variant detection is required. The goal of this study was to evaluate a recently developed assay for genetic variant detection based upon use of Surveyor nuclease, which is an endonuclease that cleaves DNA at sites of mismatches.

Materials/Methods: DNA samples were screened for genetic variants in the *TGFB1, XRCC1, XRCC3, SOD2* and *hHR21* genes. A total of 50 DNA fragments comprising each exon with flanking intronic region for the five genes of interest were analyzed using DNA isolated from blood lymphocytes derived from 32 African-American patients diagnosed with prostate cancer. These patients had been treated with either a radioactive implant alone or in combination with external beam radiotherapy. This yielded 1600 amplification products which were screened in a blinded fashion for genetic variants using both DNA sequencing and the Surveyor nuclease assay. Identification of samples possessing variants, which were treated with Surveyor nuclease, was accomplished using high-performance liquid chromatography on a Transgenomic WAVE Nucleic Acid High Sensitivity Fragment Analysis System.

Results: Through DNA sequencing, 272 samples were found to possess genetic variants. Of these, the Surveyor nuclease assay correctly identified 271 samples as having variants. For the 1328 samples that did not possess a variant, the Surveyor nuclease assay correctly assigned 1297. Thus, the sensitivity and specificity of the Surveyor nuclease assay were 99.6% and 97.7%, respectively. The positive and negative predictive powers of the assay were 89.7% and 99.9%, respectively. In addition, the Surveyor nuclease assay identified 10 samples that the initial sequencing results reported as negative due to ambiguous sequencing profiles, but upon re-sequencing proved to possess variants. The Surveyor nuclease assay also correctly identified one sample as not possessing a variant that an initial sequencing result suggested had a genetic alteration, but upon re-sequencing proved negative. Erectile function was evaluable for 27 patients. Excluding common variants from the analysis in which the minor allele was present in more than 10% of the population, it was found that 6 of 8 (75%) patients harboring at least 2 genetic variants in the five genes screened exhibited a prospective decline in erectile function. In contrast, only 3 of the 19 (16%) patients that had either 0 or 1 variants, developed erectile dysfunction following radiotherapy (p_0.006, Fisher's Exact Test).

Conclusions: The Surveyor nuclease assay represents a powerful tool for identification of genetic variants that may be predictive for the development of adverse radiotherapy effects.

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GRANTS

Sponsor: National Institute of Health Loan Repayment Program
Principle Investigator: **Cesaretti JA**
Project entitled,"ATM Heterozygosity and the Development of Radiation-Induced Erectile Dysfunction and Urinary Morbidity Following Radiotherapy for Prostate Cancer."
Total award, $65,920 over 2 years (7/1/05-6/30/07)

Sponsor: American Cancer Society
Principle Investigator: Rosenstein BA
Co-Investigator: **Cesaretti JA**
Project entitled, "Genetic Predictors of Adverse Radiotherapy Response in African-Americans." Total award, $840,000 over 4 years (7/1/05-6/30/09)

Basic Science Travel Grant
ASTRO Research Evaluation Committee
ASTRO's 46th Annual Meeting in Atlanta, GA from October 3-7, 2004

Physician Research Training Award, PCO31163, 2003,
Prostate Cancer Research Program.
Sponsor: Department of Defense.
Principle Investigator: **Cesaretti JA**
Mentors: Stock RG, Rosenstein BA

Project entitled, "ATM Heterozygosity and the Development of Radiation-Induced Erectile Dysfunction and Urinary Morbidity Following Radiotherapy for Prostate Cancer."
Total award, $700,000 over 5 years (7/1/04-6/30/09)

PUBLICATIONS

Cesaretti JA, Stone NN, Stock RG. "Urinary symptom flare following I-125 prostate brachytherapy." *Int J Radiat Oncol Biol Phys* 2003 Jul 15; 56(4):1085-92.

Stock RG, Stone NN, **Cesaretti JA**. "Prostate-specific antigen bounce after prostate seed implantation for localized prostate cancer: descriptions and implications." *Int J Radiat Oncol Biol Phys* 2003 Jun 1; 56(2):448-53.

Stock RG, Cahlon O, **Cesaretti JA**, Kollmeier MA, Stone NN. "Combined Modality Treatment in the Management of High Risk Prostate Cancer." *Int J Radiat Oncol Biol Phys* 2004 Aug 1; 59(5):1352-1359.

Cesaretti JA, Stone NN, Stock RG. "Does a prior transurethral resection of the prostate compromise brachytherapy quality: a dosimetric analysis." *Int J Radiat Oncol Biol Phys.* 2004 Oct 1; 60(2):648-653.

Cesaretti JA, Stock RG, Atencio DA, Bernstein J, Stone NN, Wallenstein S, Green S, Loeb KL, Kollmeier MA, Smith M, Rosenstein BS. "ATM sequence variants are predictive of adverse radiotherapy response among patients treated for prostate cancer." *Int J Radiat Oncol Biol Phys*. 2005 Jan 1;61(1):196-202.

Cesaretti JA, Stock RG, Stone NN. "Brachytherapy." Book Chapter, Prostate Cancer: Principles and Practice, Ed by Kirby R, Partin AW, Feneley M, Parsons JK. Taylor and Francis Medical Books.

Kollmeier MA, Stock RG, **Cesaretti JA**, Stone NN. "Urinary Morbidity Following Post-brachytherapy Transurethral Resection of the Prostate." *J Urol*. 2005 Mar;173(3):808-12.

Andreassen CN, Overgaard J, Alsner J, Overgaard M, Herskind C, **Cesaretti JA** et al. "ATM sequence variants and risk of radiation-induced subcutaneous fibrosis after postmastectomy radiotherapy." *Int J Radiat Oncol Biol Phys*. 2006 Mar 1;64(3):776-83.

Stock RG, **Cesaretti JA**, Stone NN. "Disease-specific survival following the brachytherapy management of prostate cancer." *Int J Radiat Oncol Biol Phys*. 2006 Mar 1;64(3):810-6.

Andreassen CN, Overgaard J, Alsner J, Overgaard M, Herskind C, **Cesaretti JA**, Atencio DP, Green S, Formenti SC, Stock RG, Rosenstein BS. "ATM sequence variants and risk of radiation-induced subcutaneous fibrosis after postmastectomy radiotherapy." *Int J Radiat Oncol Biol Phys*. 2006 Mar 1;64(3):776-83.

Stock RG, Stone NN, **Cesaretti JA**, Rosenstein BS. "Biologically effective dose values for prostate brachytherapy: Effects on PSA failure and post-treatment biopsy results." *Int J Radiat Oncol Biol Phys*. 2006 Feb 1;64(2):527-33.

Stock RG, Ho A, **Cesaretti JA**, Stone NN. "Changing the patterns of failure for high-risk prostate cancer patients by optimizing local control." *Int J Radiat Oncol Biol Phys*. 2006 Oct 1;66(2):389-94.

Ho AY, Atencio DP, Peters S, Stock RG, Formenti SC, **Cesaretti JA**, Green S, Haffty B, Drumea K, Leitzin L, Kuten A, Azria D, Ozsahin M, Overgaard J, Andreassen CN, Trop CS, Park J, Rosenstein BS. "Genetic predictors of adverse radiotherapy effects: the Gene-PARE project." *Int J Radiat Oncol Biol Phys*. 2006 Jul 1;65(3):646-55.

Peters CA, **Cesaretti JA**, Stone NN, Stock RG. "Brachytherapy for patients with inflammatory bowel disease." *Int J Radiat Oncol Biol Phys*. 2006 Oct 1;66(2):424-9.

Lehrer S, **Cesaretti JA**, Stone NN, Stock RG. "Urinary symptom flare after brachytherapy for prostate cancer is associated with erectile dysfunction and more urinary symptoms before implantation." *BJU Int*. 2006 Nov;98(5):979-81.

Schiff JD, Bar-Chama N, **Cesaretti J**, Stock R. "Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function." *BJU Int.* 2006 Dec;98(6):1255-8.

PRESENTATIONS

Cesaretti JA, Stone NN, Stock RG. "Late Exacerbation of Urinary Symptoms Following I-125 Prostate Brachytherapy." ASTRO 44th Annual Meeting, October 2002, New Orleans, Louisiana.

Cesaretti JA, Atencio DA, Stock RG, Stone NN, Green S, Bernstein JL, Wallenstein S, Loeb K, Chalon O, Kollmeier MA, Smith MJ, Rosenstein BA. "*ATM* Mutational Status is Associated with an Increased Severity and Earlier Onset of Radiation-Related Rectal Morbidity Among Patients Treated with ^{125}I Prostate Brachytherapy." RSNA 89th Annual Meeting, November 2003, New York, New York.

Cesaretti JA. "Interactive Ultrasound Guided Prostate Brachytherapy; The Mount Sinai Experience." First Annual Radiation Oncology Symposium, Galliera Hospital, November 2003, Genoa, Italy.

Cesaretti JA. "Real Time Brachytherapy: The American Experience." International Course on Brachytherapy, San Paolo Hospital, Febuary 2004, Savona, Italy.

Cesaretti JA. "Genetic Associations Are Predictive Of Adverse Outcomes Following Radiotherapy
For Prostate Cancer." Radiological and Medical Physics Society of New York (RAMPS), Spring Symposium Advancing Radiation Oncology Planning Through an Understanding of Biology, May 2004, New York, New York.

Cesaretti JA. "ATM Sequence Variants are Predictive of Adverse Radiotherapy Response Among Patients Treated for Prostate Cancer." ASTRO 46th Annual Meeting, October 2004, Atlanta, Georgia.

Cesaretti JA. "Intensity Modulated Radiation Therapy for Brain Malignancies." IV Advanced Techniques and Technology in Image-Guided Brain and Spine Surgery, December 5, 2004, New York, New York.

Cesaretti JA. "Radiation Therapy for Esophageal Carcinoma." From Gastroesophageal Reflux Disease to Esophageal Cancer: New Treatments and Technologies, April 2, 2005, The New York Academy of Medicine, New York, New York.

Cesaretti JA. "Intensity Modulated Radiation Therapy for Prostate Cancer" and "Combined Modality Therapy for Prostate Cancer." Advanced Workshop in the Treatment of Prostate Cancer, April 27-29, 2005, The New York Academy of Medicine, New York, New York.

Cesaretti JA. "Intensity Modulated Radiation Therapy for Prostate Cancer" and "Combined Modality Therapy for Prostate Cancer." Advanced Workshop in the Treatment of Prostate Cancer II, September 27-29, 2005, The New York Academy of Medicine, New York, New York.

Cesaretti JA. "Erectile function following prostate brachytherapy with 7 years minimum follow-up." ASTRO 47th Annual meeting, October 2005, Denver, Colorado.

Cesaretti JA. "The Genetics of Radiation Sensitivity." 11th Annual Scottsdale Prostate Cancer Symposium, March 1-5, 2006, Scottsdale, Arizona.

Cesaretti JA. "A dose volume histogram for the incidence of rectal bleeding among ATM heterozygotes." ASTRO 48th Annual meeting, November 2006, Philadelphia, Pennsylvania.